

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 213/38, A61K 31/44		A1	(11) International Publication Number: WO 97/40011 (43) International Publication Date: 30 October 1997 (30.10.97)
(21) International Application Number: PCT/US97/06398		(74) Agent: BODENHEIMER, Stephen, M., Jr.; Bell, Seltzer, Park & Gibson, P.O. Drawer 34009, Charlotte, NC 28234 (US).	
(22) International Filing Date: 16 April 1997 (16.04.97)			
(30) Priority Data: 08/631,761 23 April 1996 (23.04.96) US		(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(60) Parent Application or Grant (63) Related by Continuation US 08/631,761 (CON) Filed on 23 April 1996 (23.04.96)			
(71) Applicant (for all designated States except US): R. J. REYNOLDS TOBACCO COMPANY [US/US]; Law Department - Patents, Bowman Gray Technical Center, 950 Reynolds Boulevard, P.O. Box 1487, Winston-Salem, NC 27102 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(72) Inventors; and (75) Inventors/Applicants (for US only): CALDWELL, William, Scott [US/US]; 1270 Yorkshire Road, Winston-Salem, NC 27106 (US). DULL, Gary, Maurice [US/US]; 6025 Shallowford Road, Lewisville, NC 27023 (US). DOBSON, Grayland, Page [US/US]; 4524 Princess Drive, Winston-Salem, NC 27127 (US).			
(54) Title: PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS			
(57) Abstract			
<p>Patients susceptible to or suffering from central nervous system disorders are treated by administering effective amounts of aryl substituted aliphatic amine compounds, aryl substituted olefinic amine compounds or aryl substituted acetylenic amine compounds. A representative compound is (E)-N-methyl-5-(3-pyridinyl)-4-penten-2-amine.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

-1-

**PHARMACEUTICAL COMPOSITIONS FOR PREVENTION AND
TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS**

BACKGROUND OF THE INVENTION

The present invention relates to compounds having pharmaceutical properties, and in particular, to compounds useful for preventing and treating central nervous system (CNS) disorders. The present invention relates to a method for treating patients suffering from or susceptible to such disorders, and in particular, to a method for treating patients suffering from those disorders which are associated with neurotransmitter system dysfunction. The present invention also relates to compositions of matter useful as pharmaceutical compositions in the prevention and treatment of CNS disorders which have been attributed to neurotransmitter system dysfunction.

CNS disorders are a type of neurological disorder. CNS disorders can be drug induced; can be attributed to genetic predisposition, infection or trauma; or can be of unknown etiology. CNS disorders comprise neuropsychiatric disorders, neurological diseases and mental illnesses; and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency and/or a serotonergic deficiency. CNS disorders of relatively common occurrence include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism

-2-

including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and Tourette's syndrome.

5 Senile dementia of the Alzheimer's type (SDAT) is a debilitating neurodegenerative disease, mainly afflicting the elderly; characterized by a progressive intellectual and personality decline, as well as a loss of memory, perception, reasoning,

10 orientation and judgment. One feature of the disease is an observed decline in the function of cholinergic systems, and specifically, a severe depletion of cholinergic neurons (i.e., neurons that release acetylcholine, which is believed to be a

15 neurotransmitter involved in learning and memory mechanisms). See, Jones, et al., Intern. J. Neurosci., Vol. 50, p. 147 (1990); Perry, Br. Med. Bull., Vol. 42, p. 63 (1986) and Sitaram, et al., Science, Vol. 201, p. 274 (1978). It has been observed that nicotinic

20 acetylcholine receptors, which bind nicotine and other nicotinic agonists with high affinity, are depleted during the progression of SDAT. See, Giacobini, J. Neurosci. Res., Vol. 27, p. 548 (1990); and Baron, Neurology, Vol. 36, p. 1490 (1986). As such, it would

25 seem desirable to provide therapeutic compounds which either directly activate nicotinic receptors in place of acetylcholine or act to minimize the loss of those nicotinic receptors.

Certain attempts have been made to treat

30 SDAT. For example, nicotine has been suggested to possess an ability to activate nicotinic cholinergic receptors upon acute administration, and to elicit an increase in the number of such receptors upon chronic administration to animals. See, Rowell, Adv. Behav. Biol., Vol. 31, p. 191 (1987); and Marks, J. Pharmacol. Exp. Ther., Vol. 226, p. 817 (1983). It also has been proposed that nicotine can act directly to elicit the

-3-

release of acetylcholine in brain tissue, to improve cognitive functions, and to enhance attention. See, Rowell, et al., J. Neurochem., Vol. 43, p. 1593 (1984); Sherwood, Human Psychopharm., Vol. 8, pp. 155-184

5 5 (1993); Hodges, et al., Bio. of Nic., Edit. by Lippiello, et al., p. 157 (1991); Sahakian, et al., Br. J. Psych., Vol. 154, p. 797 (1989); and U.S. Patent Nos. 4,965,074 to Leeson and 5,242,935 to Lippiello et al. Other methods for treating SDAT have been
10 proposed, including U.S. Patent Nos. 5,212,188 to Caldwell et al. and 5,227,391 to Caldwell et al. and European Patent Application No. 588,917. Another proposed treatment for SDAT is Cognex, which is a capsule containing tacrine hydrochloride, available
15 from Parke-Davis Division of Warner-Lambert Company, which reportedly preserves existing acetylcholine levels in patients treated therewith.

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown
20 etiology, characterized by tremors and muscular rigidity. A feature of the disease appears to involve the degeneration of dopaminergic neurons (i.e., which secrete dopamine). One symptom of the disease has been observed to be a concomitant loss of nicotinic
25 receptors which are associated with such dopaminergic neurons, and which are believed to modulate the process of dopamine secretion. See, Rinne, et al., Brain Res., Vol. 54, pp. 167-170 (1991) and Clark, et al., Br. J. Pharm., Vol. 85, pp. 827-835 (1985). It also has been
30 proposed that nicotine can ameliorate the symptoms of PD. See, Smith et al., Rev. Neurosci., Vol. 3(1), pp. 25-43 (1982).

Certain attempts have been made to treat PD. One proposed treatment for PD is Sinemet CR, which is a
35 sustained-release tablet containing a mixture of carbidopa and levodopa, available from The DuPont Merck Pharmaceutical Co. Another proposed treatment for PD

-4-

is Eldepryl, which is a tablet containing selegiline hydrochloride, available from Somerset Pharmaceuticals, Inc. Another proposed treatment for PD is Parlodel, which is a tablet containing bromocriptine mesylate,

5 available from Sandoz Pharmaceuticals Corporation.

Another method for treating PD and a variety of other neurodegenerative diseases has been proposed in U.S.

Patent No. 5,210,076 to Berliner et al.

Tourette's syndrome (TS) is an autosomal dominant neuropsychiatric disorder characterized by a range of neurological and behavioral symptoms. Typical symptoms include (i) the onset of the disorder before the age of 21 years, (ii) multiple motor and phonic tics although not necessarily concurrently, (iii)

15 variance in the clinical phenomenology of the tics, and (iv) occurrence of quasi daily tics throughout a period of time exceeding a year. Motor tics generally include eye blinking, head jerking, shoulder shrugging and facial grimacing; while phonic or vocal tics include

20 throat clearing, sniffling, yelping, tongue clicking and uttering words out of context. The pathophysiology of TS presently is unknown, however it is believed that neurotransmission dysfunction is implicated with the disorder. See, Calderon-Gonzalez et al., Intern.

25 Pediat., Vol. 8(2), pp. 176-188 (1993) and Oxford Textbook of Medicine, Eds. Weatherall et al., Chapter 21.218 (1987).

It has been proposed that nicotine pharmacology is beneficial in suppressing the symptoms associated with TS. See, Devor et al., The Lancet, Vol. 8670, p. 1046 (1989); Jarvik, British J. of Addiction, Vol. 86, pp. 571-575 (1991); McConville et al., Am. J. Psychiatry, Vol. 148 (6), pp. 793-794 (1991); Newhouse et al., Brit. J. Addic., Vol. 86, pp. 35 521-526 (1991); McConville et al., Biol. Psychiatry, Vol. 31, pp. 832-840 (1992); and Sanberg et al., Proceedings from Intl. Symp. Nic., S39 (1994). It also

-5-

has been proposed to treat TS using Haldol, which is haloperidol available from McNeil Pharmaceutical; Catapres, which is clonidine available from Boehringer Ingelheim Pharmaceuticals, Inc.; Orap, which is

5 pimozide available from Gate Pharmaceuticals; Prolixin, which is fluphenazine available from Apothecon Division of Bristol-Myers Squibb Co.; and Klonopin, which is clonazepam available from Hoffmann-LaRoche Inc.

Attention deficit disorder (ADD) is a

10 disorder which affects mainly children, although ADD can affect adolescents and adults. See, Vinson, Arch. Fam. Med., Vol. 3(5), pp. 445-451 (1994); Hechtman., J. Psychiatry Neurosci., Vol. 19 (3), pp. 193-201 (1994); Faraone et al., Biol. Psychiatry, Vol. 35(6), pp. 15 398-402 (1994) and Malone et al., J. Child Neurol., Vol. 9(2), pp. 181-189 (1994). Subjects suffering from the disorder typically have difficulty concentrating, listening, learning and completing tasks; and are restless, fidgety, impulsive and easily distracted.

20 Attention deficit disorder with hyperactivity (ADHD) includes the symptoms of ADD as well as a high level of activity (e.g., restlessness and movement). Attempts to treat ADD have involved administration of Dexedrine, which is a sustained release capsule containing

25 dextroamphetamine sulfate, available from SmithKline Beecham Pharmaceuticals; Ritalin, which is a tablet containing methylphenidate hydrochloride, available from Ciba Pharmaceutical Company; and Cylert, which is a tablet containing pemoline, available from Abbott

30 Laboratories. In addition, it has been reported that administration of nicotine to an individual improves that individual's selective and sustained attention. See, Warburton et al., Cholinergic control of cognitive resources Neuropsychobiology, Eds. Mendlewicz, et al., 35 pp 43-46 (1993).

Schizophrenia is characterized by psychotic symptoms including delusions, catatonic behavior and

-6-

prominent hallucinations, and ultimately results in a profound decline in the psychosocial affect of the subject suffering therefrom. Traditionally, schizophrenia has been treated with Klonopin, which is
5 available as a tablet containing clonazepam, available from Hoffmann-LaRoche Inc.; Thorazine, which is available as a tablet containing chlorpromazine, available from SmithKline Beecham Pharmaceuticals; and Clozaril, which is a tablet containing clozapine,
10 available from Sandoz Pharmaceuticals. Such neuroleptics are believed to be effective as a result of interaction thereof with the dopaminergic pathways of the CNS. In addition, a dopaminergic dysfunction possessed by individuals suffering from schizophrenia
15 has been proposed. See, Lieberman et al., Schizophr. Bull., Vol. 19, pp. 371-429 (1993) and Glassman, Amer. J. Psychiatry, Vol. 150, pp. 546-553 (1993). Nicotine has been proposed as being effective in effecting neurotransmitter dysfunction associated with
20 schizophrenia. See, Merriam et al., Psychiatr. Annals, Vol. 23, pp. 171-178 (1993) and Adler et al., Biol. Psychiatry, Vol. 32, pp. 607-616 (1992).

Nicotine has been proposed to have a number of pharmacological effects. Certain of those effects
25 may be related to effects upon neurotransmitter release. See, for example, Sjak-shie et al., Brain Res., Vol. 624, pp. 295-298 (1993), where neuroprotective effects of nicotine are proposed. Release of acetylcholine and dopamine by neurons upon
30 administration of nicotine has been reported by Rowell et al., J. Neurochem., Vol. 43, pp. 1593-1598 (1984); Rapier et al., J. Neurochem., Vol. 50, pp. 1123-1130 (1988); Sandor et al., Brain Res., Vol. 567, pp. 313-316 (1991) and Vizi, Br. J. Pharmacol., Vol. 47, pp. 765-777 (1973). Release of norepinephrine by neurons upon administration of nicotine has been reported by Hall et al., Biochem. Pharmacol., Vol. 21,

-7-

pp. 1829-1838 (1972). Release of serotonin by neurons upon administration of nicotine has been reported by Hery et al., Arch. Int. Pharmacodyn. Ther., Vol. 296, pp. 91-97 (1977). Release of glutamate by neurons upon 5 administration of nicotine has been reported by Toth et al., Neurochem Res., Vol. 17, pp. 265-271 (1992). Therefore, it would be desirable to provide a pharmaceutical composition containing an active ingredient having nicotinic pharmacology, which 10 pharmaceutical composition is capable of illiciting neurotransmitter release within a subject in order to prevent or treat a neurological disorder. In addition, nicotine reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used 15 for the treatment of certain CNS disorders. See, Sanberg et al., Pharmacol. Biochem. & Behavior, Vol. 46, pp. 303-307 (1993); Harsing et al., J. Neurochem., Vol. 59, pp. 48-54 (1993) and Hughes, Proceedings from Intl. Symp. Nic., S40 (1994). Furthermore, various 20 other beneficial pharmacological effects of nicotine have been proposed. See, Decina et al., Biol. Psychiatry, Vol. 28, pp. 502-508 (1990); Wagner et al., Pharmacopsychiatry, Vol. 21, pp. 301-303 (1988); Pomerleau et al., Addictive Behaviors, Vol. 9, p. 265 25 (1984); Onaivi et al., Life Sci., Vol. 54(3), pp. 193-202 (1994) and Hamon, Trends in Pharmacol. Res., Vol. 15, pp. 36-39.

It would be desirable to provide a useful method for the prevention and treatment of a CNS 30 disorder by administering a nicotinic compound to a patient susceptible to or suffering from such a disorder. It would be highly beneficial to provide individuals suffering from certain CNS disorders with interruption of the symptoms of those diseases by the 35 administration of a pharmaceutical composition which has nicotinic pharmacology and which has a beneficial effect upon the functioning of the CNS, but which does

-8-

not provide any significant associated side effects (e.g., increased heart rate and blood pressure) attendant with interaction of that compound with cardiovascular sites. It would be highly desirable to

- 5 provide a pharmaceutical composition incorporating a compound which interacts with nicotinic receptors which have the potential to affect the functioning of the CNS, but which does not significantly affect those receptors which have the potential to induce
- 10 undesirable side effects (e.g., appreciable pressor cardiovascular effects and appreciable activity at skeletal muscle sites).

SUMMARY OF THE INVENTION

The present invention relates to aryl substituted aliphatic amine compounds, aryl substituted olefinic amine compounds and aryl substituted acetylenic amine compounds. A representative compound is (E)-N-methyl-5-(3-pyridinyl)-4-penten-2-amine.

The present invention relates to a method for providing prevention or treatment of a central nervous system (CNS) disorder. The method involves administering to a subject an effective amount of a compound of the present invention.

The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of a compound of the present invention. Such a pharmaceutical composition incorporates a compound which has the capability of interacting with relevant nicotinic receptor sites of a subject, and hence has the capability of acting as a therapeutic in the prevention or treatment of a CNS disorder.

The pharmaceutical compositions of the present invention are useful for the prevention and treatment of CNS disorders. The pharmaceutical compositions provide therapeutic benefit to individuals

-9-

suffering from certain CNS disorders and exhibiting clinical manifestations of such disorders in that the compounds within those compositions have the potential to (i) exhibit nicotinic pharmacology and affect

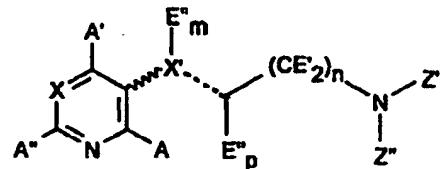
5 nicotinic receptors sites in the CNS (e.g., act as a pharmacological agonist to activate nicotinic receptors), and (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases. In addition, the compounds are

10 expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) not provide appreciable adverse side effects (e.g., significant increases in blood pressure and

15 heart rate, and significant effects upon skeletal muscle). The pharmaceutical compositions of the present invention are believed to be safe and effective with regards to prevention and treatment of CNS disorders.

20 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention, in one aspect, relates to certain compounds having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater

25 than 0, often greater than 0.1, generally greater than 0.2 and even greater than 0.3; less than 0 and generally less than -0.1; or 0; as determined in accordance with Hansch et al., Chem. Rev., Vol. 91, pp. 165-195 (1991); n is an integer which is 1, 2, 3, 4, 5,

-10-

6 or 7, preferably is 1, 2 or 3, and most preferably is 2 or 3; E' represents hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C₁ - C₅, such as methyl, ethyl or isopropyl) or halo substituted

5 lower alkyl (e.g., straight chain or branched alkyl including C₁ - C₅ such as trifluormethyl or trichloromethyl); E'' represents lower alkyl (e.g., straight chain or branched alkyl including C₁ - C₅, such as methyl, ethyl or isopropyl) or halo substituted

10 lower alkyl (e.g., straight chain or branched alkyl including C₁ - C₅, such as trifluormethyl or trichloromethyl); Z' and Z'' individually represent hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C₁ - C₅, such as methyl, ethyl

15 or isopropyl), and preferably at least one of Z' and Z'' is hydrogen, and most preferably Z' is hydrogen and Z'' is methyl; alternatively Z' is hydrogen and Z'' represents a ring structure, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

20 adamantlyl, quinuclidinyl, pyridinyl, quinolinyl, pyrnidinyl, phenyl, alkyl or halo substituted phenyl, benzyl, or alkyl or halo substituted benzyl; alternatively Z', Z'' and the associated nitrogen atom can form a ring structure, such as aziridinyl,

25 azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; A, A' and A'' individually represent hydrogen, alkyl (e.g., lower straight chain or branched alkyl, including C₁ - C₅, but preferably methyl or ethyl) or halo (e.g., F, Cl, Br or I); the dashed line

30 in the structure represents a C-C single bond, a C-C double bond or a C-C triple bond; m is 0 or 1 when the dashed line is a C-C single or C-C double bond, and 0 when the dashed line is a C-C triple bond; p is 0 or 1 when the dashed line is a C-C single or C-C double

35 bond, and 0 when the dashed line is a C-C triple bond; the wavy line in the structure represents a cis (Z) or trans (E) form of the compound when the dashed line is

-11-

a C-C double bond; and X' represents CH₂ ($m=0$) or CHE'' ($m=1$) when the dashed line is a C-C single bond, CH or CE'' when the dashed line is a C-C double bond, and C when the dashed line is a C-C triple bond. X includes

5 N, C-H, C-F, C-Cl, C-Br, C-I, C-NR'R'', C-CF₃, C-OH, C-CN, C-C₂R', C-SH, C-SCH₃, C-N₃, C-SO₂CH₃, C-OR', C-SR', C-C(=O)N R'R'', C-NR'C(=O)R', C-(C=O)R', C-C(=O)OR', -CCH₂OR', C-OC(=O)R', COC(=O)NR'R'' and C-NR'C(=O)OR' where R' and R'' are individually hydrogen, lower alkyl

10 (e.g., alkyl containing one to five carbon atoms, preferably methyl, ethyl or isopropyl), an aromatic group-containing species or a substituted aromatic group-containing species. When X represents a carbon atom bonded to a substituent species, that substituent

15 species often has a sigma m value which is between about -0.3 and about 0.75, and frequently between about -0.25 and about 0.6. In certain circumstances when X represents a carbon atom bonded to a substituent species, the dashed line is a C-C double bond and the

20 compound has the trans (E) form, the substituent species is characterized as having a sigma m value not equal to 0. Particularly when the dashed line is a C-C double bond, the compound has the trans (E) form, A, A', A'' and Z' all are hydrogen, n is 2, and Z'' is

25 hydrogen or methyl, the substituent species is characterized as having a sigma m value not equal to 0. Particularly when the dashed line is a C-C double bond, the compound has the trans (E) form, A, A', A'' and Z' all are hydrogen, n is 2, and Z'' is hydrogen or

30 methyl, at least one of E' or E'' is lower alkyl or halo substituted lower alkyl. In addition, it is highly preferred that A is hydrogen, it is preferred that A' is hydrogen, and normally A'' is hydrogen. Generally, both A and A' are hydrogen; sometimes A and

35 A' are hydrogen, and A'' is methyl or ethyl; and often A, A' and A'' are all hydrogen. Depending upon the identity and positioning of each individual E' or E'',

-12-

certain compounds can be optically active. Typically, the values of each of m and p, and the selection of E', are such that up to about 4, and frequently up to 3, of the substituents designated as E' and E'' are

5 non-hydrogen substituents (i.e., substituents such as lower alkyl or halo-substituted lower alkyl).

Representative compounds are

N-methyl-4-(3-pyridinyl)-2-methylbutan-1-amine,

N-methyl-4-(3-pyridinyl)-3-methylbutan-1-amine,

10 N-methyl-5-(3-pyridinyl)-pentan-1-amine,

N-methyl-6-(3-pyridinyl)-hexan-3-amine,

N-methyl-5-(3-pyridinyl)-2-methylpentan-2-amine,

N-methyl-5-(3-pyridinyl)-3-methylpentan-2-amine,

N-methyl-5-(3-pyridinyl)-pentan-2-amine,

15 N-methyl-5-(3-pyridinyl)-1,1,1-trifluoropentan-2-amine,

N-methyl-5-(3-pyridinyl)-4-methylpentan-1-amine,

N-methyl-5-(3-pyridinyl)-4-methylpentan-2-amine,

N-methyl-1-(3-pyridinyl)-octan-4-amine,

N-methyl-1-(3-pyridinyl)-5-methylheptan-4-amine,

20 N-methyl-6-(3-pyridinyl)-2,4-dimethylhexan-2-amine,

N-methyl-6-(3-pyridinyl)-5-methylhexan-2-amine,

N-methyl-6-(3-pyridinyl)-hexan-2-amine,

N-methyl-6-(3-pyridinyl)-5-methylhexan-3-amine,

4-(3-pyridinyl)-2-methylbutan-1-amine,

25 4-(3-pyridinyl)-3-methylbutan-1-amine,

5-(3-pyridinyl)-pentan-1-amine,

6-(3-pyridinyl)-hexan-3-amine,

5-(3-pyridinyl)-2-methylpentan-2-amine,

5-(3-pyridinyl)-3-methylpentan-2-amine,

30 5-(3-pyridinyl)-pentan-2-amine,

5-(3-pyridinyl)-1,1,1-trifluoropentan-2-amine,

5-(3-pyridinyl)-4-methylpentan-1-amine,

5-(3-pyridinyl)-4-methylpentan-2-amine,

1-(3-pyridinyl)-octan-4-amine,

35 1-(3-pyridinyl)-3-methylheptan-5-amine,

6-(3-pyridinyl)-2,4-dimethylhexan-2-amine,

6-(3-pyridinyl)-5-methylhexan-2-amine,

-13-

6-(3-pyridinyl)-hexan-2-amine and
6-(3-pyridinyl)-5-methylhexan-3-amine.

Other representative compounds are

N-methyl-5-(3-pyridinyl)-4-pentyn-2-amine,

5 N-methyl-6-(3-pyridinyl)-5-hexyn-3-amine,

N-methyl-1-(3-pyridinyl)-1-heptyn-4-amine,

N-methyl-1-(3-pyridinyl)-1-octyn-4-amine,

N-methyl-1-(3-pyridinyl)-1-nonyn-4-amine,

N-methyl-5-(3-pyridinyl)-3-methyl-4-pentyn-2-amine,

10 5-(3-pyridinyl)-4-pentyn-2-amine,

6-(3-pyridinyl)-5-hexyn-3-amine,

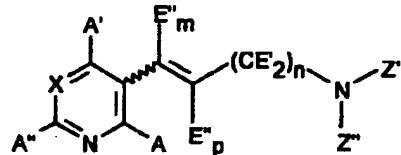
1-(3-pyridinyl)-1-heptyn-4-amine,

1-(3-pyridinyl)-1-octyn-4-amine,

1-(3-pyridinyl)-1-nonyn-4-amine and

15 5-(3-pyridinyl)-3-methyl-4-pentyn-2-amine.

Of particular interest are compounds having the formula:



where n, m, p, X, A, A', A'', E'', Z' and Z'' are as defined hereinbefore, and those compounds can have
 20 the cis (Z) or trans (E) form. For such compounds of particular interest, X most preferably is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, generally greater than 0.2 and even greater than 0.3; less than 0 and generally less than -0.1; or 0. One representative compound is
 (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine for which X is C-OCH₂CH₃, n is 2, m is 0, p is 0, A, A', A'' and Z' each are hydrogen, all E' are hydrogen and
 30 Z'' is methyl. Another representative compound is

-14-

(E)-4-[3-(5-methoxypyridin)yl]-3-buten-1-amine for which X is C-OCH₃, n is 2, m is 0, p is 0, all E' are hydrogen, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is

5 (E)-N-methyl-4-[3-(5-methoxypyridin)yl]-3-buten-1-amine for which X is C-OCH₃, n is 2, m is 0, p is 0, all E' are hydrogen, and A, A', A'', and Z' are each hydrogen, and Z'' is methyl. Another representative compound is

10 (E)-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine for which X is C-OCH₂CH₃, n is 2, m is 0, p is 0, all E' are hydrogen, and A, A', A'', Z' and Z'' each are hydrogen. Another representative compound is (E)-4-[3-(5-methoxy-6-methylpyridin)yl]-3-buten-1-amine for which X is C-OCH₃, n is 2, m is 0, p is 0, all E' are hydrogen, A'' is methyl, and A, A', Z' and Z'' each are hydrogen.

15 Another representative compound is

(E)-N-methyl-4-[3-(5-methoxy-6-methylpyridin)yl]-3-buten-1-amine for which X is C-OCH₃,

20 n is 2, m is 0, p is 0, all E' are hydrogen, A'' and Z'' each are methyl, and A, A' and Z' each are hydrogen. Another representative compound is

(E)-N-methyl-4-[3-(5-hydroxymethylpyridin)yl]-3-buten-1-amine for which X is -CCH₂OH, n is 2, m is 0, p is 0, all E' are hydrogen, Z' is methyl and A, A', A'' and Z'' each are hydrogen.

25 Other representative compounds are (E) and (Z)-N-methyl-4-(3-pyridinyl)-2-methyl-3-buten-1-amine, (E) and

30 (Z)-N-methyl-4-(3-pyridinyl)-3-methyl-3-buten-1-amine, (E) and (Z)-N-methyl-6-(3-pyridinyl)-5-hexen-3-amine, (E) and (Z)-N-methyl-5-(3-pyridinyl)-2-methyl-4-penten-2-amine, (E) and (Z)-N-methyl-5-(3-pyridinyl)-3-methyl-4-penten-2-amine,

35 (E) and (Z)-N-methyl-5-(3-pyridinyl)-4-penten-2-amine, (E) and (Z)-N-methyl-5-(3-pyridinyl)-1,1,1-trifluoro-4-penten-2

-15-

-amine, (E) and (Z)-

N-methyl-5-(3-pyridinyl)-4-methyl-4-penten-1-amine, (E) and (Z)-N-methyl-5-(3-pyridinyl)-4-methyl-4-penten-2-amine, (E) and (Z)-N-methyl-1-(3-pyridinyl)-1-octen-4-amine, (E) and (Z)-N-methyl-1-(3-pyridinyl)-5-methyl-1-hepten-4-amine, (E) and (Z)-N-methyl-6-(3-pyridinyl)-2,4-dimethyl-5-hexen-2-amine, (E) and (Z)-N-methyl-6-(3-pyridinyl)-5-methyl-5-hexen-2-amine, (E) and (Z)-N-methyl-6-(3-pyridinyl)-5-methyl-5-hexen-3-amine, (E) and (Z)-4-(3-pyridinyl)-2-methyl-3-buten-1-amine, (E) and (Z)-4-(3-pyridinyl)-3-methyl-3-buten-1-amine, (E) and (Z)-6-(3-pyridinyl)-5-hexen-3-amine, (E) and (Z)-5-(3-pyridinyl)-2-methyl-4-penten-2-amine, (E) and (Z)-5-(3-pyridinyl)-3-methyl-4-penten-2-amine, (E) and (Z)-5-(3-pyridinyl)-4-penten-2-amine, (E) and (Z)-5-(3-pyridinyl)-1,1,1-trifluoro-4-penten-2-amine, (E) and (Z)-5-(3-pyridinyl)-4-methyl-4-penten-1-amine, (E) and (Z)-5-(3-pyridinyl)-4-methyl-4-penten-2-amine, (E) and (Z)-1-(3-pyridinyl)-1-octen-4-amine, (E) and (Z)-1-(3-pyridinyl)-3-methyl-5-hepten-1-amine, (E) and (Z)-6-(3-pyridinyl)-2,4-dimethyl-5-hexen-2-amine, (E) and (Z)-6-(3-pyridinyl)-5-methyl-5-hexen-2-amine, (E) and (Z)-6-(3-pyridinyl)-5-methyl-5-hexen-3-amine. For such representative compounds at least one of m or p are 1 and/or at least one of E' is a non-hydrogen substituent. The manner in which aryl substituted aliphatic amine compounds of the present invention are synthetically produced can vary. Preparation of various aryl substituted aliphatic amine compounds can be carried out using the types of techniques disclosed by Rondahl, Acta Pharm. Suec., Vol. 13, pp. 229-234 (1976). Certain metanicotine-type compounds that possess a saturated side chain rather than an olefinic

-16-

side chain can be prepared by hydrogenation of the corresponding metanicotine-type compounds or the corresponding acetylenic precursors. For example, a dihydrometanicotine-type compound can be prepared by 5 hydrogenation of an (E)-metanicotine-type compound using the types of procedures described by Kamimura et al., Agr. Biol. Chem., Vol. 27, No. 10, pp. 684-688 (1963).

The manner in which aryl substituted 10 acetylenic amine compounds of the present invention are synthetically produced can vary. For example, an aryl substituted acetylenic amine compound, such as an N-methyl-4-(3-pyridinyl)-3-butyn-1-amine type compound, can be prepared using a series of synthetic steps: (i) 15 conversion of 3-pyridinecarboxaldehyde to a 1,1-dihalo-2-(3-pyridinyl)-ethylene using a carbon tetrahalide and triphenylphosphine, (ii) side chain elaboration of this intermediate by reaction with butyl lithium and ethylene oxide, affording 4-(3 20 pyridinyl)-3-butyn-1-ol, (iii) conversion of this intermediate to its methanesulfonate ester, and (iv) mesylate displacement with methyl amine, affording an N-methyl-4-(3-pyridinyl)-3-butyn-1-amine type compound. Representative synthetic techniques for aryl 25 substituted acetylenic compounds are set forth in U.S. Patent Application Serial No. 08/364,979, filed January 6, 1995, the disclosure of which is incorporated herein by reference. Representative alkylene oxides which can be employed include propylene oxide, 1,2-epoxybutane, 30 1,2-epoxypentane, 1,2-epoxyhexane, 1,2-epoxyheptane, (E)-2,3-epoxybutane and (Z)-2,3-epoxybutane. 5-Substituted-3 pyridinecarboxaldehydes, such as 5-ethoxy-3-pyridinecarboxaldehyde, also can be employed.

35 The manner in which aryl substituted olefinic amine compounds of the present invention are synthetically produced can vary. (E)-metanicotine-type

-17-

compounds can be prepared using the techniques set forth by Löffler et al., Chem. Ber., Vol. 42, pp. 3431-3438 (1909) and Laforge, J.A.C.S., Vol. 50, p. 2477 (1928) from substituted nicotine-type compounds.

- 5 Certain 6-substituted metanicotine-type compounds can be prepared from the corresponding 6-substituted nicotine-type compounds using the general methods of Acheson et al., J. Chem. Soc., Perkin Trans. 1, Vol. 2, pp. 579-585 (1980). The requisite precursors for such
- 10 compounds, 6-substituted nicotine-type compounds, can be synthesized from 6-substituted nicotinic acid esters using the general methods disclosed by Rondahl, Acta Pharm. Suec., Vol. 14, pp. 113-118 (1977). Preparation of certain 5-substituted metanicotine-type compounds
- 15 can be accomplished from the corresponding 5-substituted nicotine-type compounds using the general method taught by Acheson et al., J. Chem. Soc. Perkin Trans. 1, Vol. 2, pp. 579-585 (1980). The 5-halo-substituted nicotine-type compounds (e.g.,
- 20 fluoro and bromo-substituted nicotine-type compounds) and the 5-amino nicotine-type compounds can be prepared using the general procedures disclosed by Rondahl, Acta Pharm. Suec., Vol. 14, pp. 113-118 (1977). The 5-trifluoromethyl nicotine-type compounds can be
- 25 prepared using the techniques and materials set forth in Ashimori et al., Chem. Pharm. Bull., Vol. 38(9), pp. 2446-2458 (1990) and Rondahl, Acta Pharm. Suec., Vol. 14, pp. 113-118 (1977).

Furthermore, preparation of certain

- 30 metanicotine-type compounds can be accomplished using a palladium catalyzed coupling reaction of an aromatic halide and a terminal olefin containing a protected amine substituent, removal of the protective group to obtain a primary amine, and optional alkylation to
- 35 provide a secondary or tertiary amine. In particular, certain metanicotine-type compounds can be prepared by subjecting a 3-halo-substituted, 5-substituted pyridine

-18-

compound or a 5-halo substituted pyrimidine compound to a palladium catalyzed coupling reaction using an olefin possessing a protected amine functionality (e.g., such an olefin provided by the reaction of a phthalimide

5 salt with 3-halo-1-propene, 4-halo-1-butene, 5-halo-1-pentene or 6-halo-1-hexene). See, Frank et al., J. Org. Chem., Vol. 43(15), pp. 2947-2949 (1978) and Malek et al., J. Org. Chem., Vol. 47, pp. 5395-5397 (1982). Alternatively, certain metanicotine-type compounds can
10 be prepared by coupling an N-protected, modified amino acid residue, such as 4-(N-methyl-N-tert-butyloxycarbonyl)aminobutyric acid methyl ester, with an aryl lithium compound, as can be derived from a suitable aryl halide and butyl lithium. The resulting
15 N-protected aryl ketone is then chemically reduced to the corresponding alcohol, converted to the alkyl halide, and subsequently dehydrohalogenated to introduce the olefin functionality. Removal of the N-protecting group then affords the desired
20 metanicotine-type compound.

There are a number of different methods for providing (Z)-metanicotine-type compounds. In one method, (Z)-metanicotine-type compounds can be synthesized from nicotine-type compounds as a mixture
25 of E and Z isomers; and the (Z)-metanicotine-type compounds can then be separated by chromatography using the types of techniques disclosed by Sprouse et al., Abstracts of Papers, p. 32, Coresta/TCRC Joint Conference (1972). In another method,
30 metanicotine-type compounds can be prepared by the controlled hydrogenation of the corresponding acetylenic compound (e.g., an N-methyl-4-(3-pyridinyl)-3-butyn-1-amine type compound). For example, certain 5-substituted
35 (Z)-metanicotine-type compounds and certain 6-substituted (Z)-metanicotine-type compounds can be prepared from 5-substituted-3-pyridinecarboxaldehydes

-19-

and 6-substituted-3-pyridinecarboxaldehydes, respectively. Representative synthetic techniques for (Z)-metanicotine-type compounds are set forth in U.S. Patent Application Serial No. 08/364,979.

5 There are yet other methods by which aryl substituted olefinic amine compounds of the present invention can be synthetically produced. An olefinic alcohol, such as 5-hexen-2-ol, is condensed with an aromatic halide, such as 3-bromopyridine or

10 3-iodopyridine. Typically, the types of procedures set forth in Frank et al., J. Org. Chem., Vol. 43, pp. 2947-2949 (1978) and Malek et al., J. Org. Chem., Vol. 47, pp. 5395-5397 (1982) involving a palladium-catalyzed coupling of an olefin and an

15 aromatic halide are used. The olefinic alcohol optionally can be protected as a t-butyldimethylsilyl ether prior to the coupling. Desilylation then produces the olefinic alcohol. The alcohol condensation product then is converted to an amine

20 using the type of procedures set forth in deCosta et al., J. Org. Chem., Vol. 35, pp. 4334-4343 (1992). Typically, the alcohol condensation product is converted to the aryl substituted olefinic amine by activation of the alcohol using methanesulfonyl

25 chloride or p-toluenesulfonyl chloride, followed by mesylate or tosylate displacement using ammonia, or a primary or secondary amine. Thus, when the amine is ammonia, an aryl substituted olefinic primary amine compound is provided; when the amine is a primary amine

30 such as methylamine or cyclobutylamine, an aryl substituted olefinic secondary amine compound is provided; and when the amine is a secondary amine such as dimethylamine or pyrrolidine, an aryl substituted olefinic tertiary amine compound is provided. Other

35 representative olefinic alcohols include 4-penten-2-ol, 4-penten-1-ol, 5-hexen-3-ol, 3-methyl-3-buten-1-ol, 2-methyl-3-buten-1-ol, 2-methyl-

-20-

4-penten-2-ol, 4-methyl-4-penten-1-ol,
4-methyl-4-penten-2-ol, 1-octen-4-ol, 5-
methyl-1-hepten-4-ol, 4-methyl-5-hexen-2-ol, 5
-methyl-5-hexen-2-ol, 5-hexen-2-ol and
5 5-methyl-5-hexen-3-ol. Trifluormethyl-substituted
olefinic alcohols, such as 1,1,1
-trifluoro-4-penten-2-ol, can be prepared from 1
-ethoxy-2,2,2-trifluoro-ethanol and
allyltrimethylsilane using the procedures of Kubota et
10 al., Tetrahedron Letters, Vol. 33(10), pp. 1351-1354
(1992), or from trifluoroacetic acid ethyl ester and
allyltributylstannane using the procedures of Ishihara
et al., Tetrahedron Letters, Vol. 34(56), pp. 5777-5780
(1993). Certain olefinic alcohols are optically
15 active, and can be used as enantiomeric mixtures or as
pure enantiomers in order to provide the corresponding
optically active forms of aryl substituted olefinic
amine compounds. When an olefinic allylic alcohol,
such as methallyl alcohol, is reacted with an aromatic
20 halide, an aryl substituted olefinic aldehyde is
produced; and the resulting aldehyde can be converted
to an aryl substituted olefinic amine compound by
reductive amination (e.g., by treatment using an alkyl
amine and sodium cyanoborohydride). Preferred aromatic
25 halides are 3-bromopyridine-type compounds and
3-iodopyridine-type compounds. Typically, substituent
groups of such 3-halopyridine-type compounds are such
that those groups can survive contact with those
chemicals (e.g., tosylchloride and methylamine) and the
30 reaction conditions experienced during the preparation
of the aryl substituted olefinic amine compound.
Alternatively, substituents such as -OH, -NH₂ and -SH
can be protected as corresponding acyl compounds, or
substituents such as -NH₂ can be protected as a
35 phthalimide functionality.

The compounds of the present invention can be
employed in a free base form or in a salt form (e.g.,

-21-

as pharmaceutically acceptable salts, such as chloride, perchlorate, ascorbate, sulfate, tartrate, fumarate, citrate, malate, lactate or aspartate salts). One method for providing the compound in salt form is set forth in U.S. Patent Application Serial No. 08/364,979. Another method for providing the compound in a fumaric salt form involves (i) dissolving one equivalent of the compound in ethanol, (ii) mixing the solution with two equivalents of fumaric acid, (iii) concentrating the resulting solution to dryness, (iv) dissolving the resulting solid in ethanol, and then (v) precipitating the monofumarate salt from the ethanol. Another method for providing the compound in a fumaric salt form involves (i) adding a solution of suitably pure compound dissolved in tetrahydrofuran to a refluxing solution of fumaric acid in a tetrahydrofuran/ethanol co-solvent mixture to form a precipitate, (ii) applying heat and additional ethanol to the mixture to dissolve the precipitate, (iii) cooling the resulting solution, and seeding the solution if necessary, to cause precipitation of salt, and (iv) filtering and collecting the salt.

The present invention relates to a method for providing prevention of a CNS disorder to a subject susceptible to such a disorder, and for providing treatment to a subject suffering from a CNS disorder. In particular, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of the CNS disorder (i.e., provide protective effects), amelioration of the symptoms of the CNS disorder, and amelioration of the reoccurrence of the CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are

-22-

set forth hereinbefore. Optically active compounds can be employed as racemic mixtures or as enantiomers. CNS disorders which can be treated in accordance with the present invention include presenile dementia (early

5 onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia and

10 Tourette's syndrome.

The pharmaceutical composition also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant

15 circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anaesthetics,

20 steroids and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of

25 administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular CNS disorder.

30 The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to

35 Brooks et al.); topically (e.g., in lotion form); orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid

-23-

carrier); intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); or

- 5 transdermally (e.g., using a transdermal patch). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective
- 10 administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. As another example, the compounds can
- 15 be delivered transdermally using the types of patch technologies available from Ciba-Geigy Corporation and Alza Corporation. The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous,
- 20 constant or controlled rate to a warm-blooded animal, such as a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the
- 25 pharmaceutical formulation interact with receptor sites within the body of the subject that effect the functioning of the CNS.

The dose of the compound is that amount effective to prevent occurrence of the symptoms of the

- 30 disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective
- 35 prevention or treatment of the disorder. Thus, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to

-24-

bind to relevant receptor sites in the brain of the subject, and to elicit neuropharmacological effects (e.g., elicit neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). Prevention of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 mg / 24 hr. / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg / 24 hr. / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/ml, and frequently does not exceed 100 ng/ml.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds useful in carrying out the present invention generally are greater than 0, often are greater than about 0.5, and frequently are greater than about 1. The log P values of such typical compounds generally are less than about 3.0, and

-25-

generally are less than about 2.5. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. See, Hansch, et al., J. Med. Chem., Vol. 11, 5 p. 1 (1968).

The compounds useful according to the method of the present invention have the ability to bind to, and cause activation of, nicotinic cholinergic receptors of the brain of the patient. As such, such 10 compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of typical compounds useful in carrying out the present invention generally exceed about 1 nM, and often exceed about 5 15 nM. The receptor binding constants of such typical compounds generally are less than about 10 μ M, often are less than about 1 μ M, and frequently are less than about 100 nM. Receptor binding constants provide a measure of the ability of the compound to bind to half 20 of the relevant receptor sites of certain brain cells of the patient. See, Cheng, et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

The compounds useful according to the method of the present invention have the ability to 25 demonstrate a nicotinic function by effectively eliciting ion flux through, and neurotransmitter secretion from, nerve ending preparations (i.e., thalamic or striatal synaptosomes). As such, such compounds have the ability to cause relevant neurons to 30 become activated, and to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, typical compounds useful in carrying out the present invention effectively provide for relevant receptor activation in amounts of at least about 30 35 percent, often at least about 50 percent, and frequently at least about 75 percent, of that maximally provided by (S)-(-)-nicotine. Generally, typical

-26-

compounds useful in carrying out the present invention are more potent than (S)-(-)-nicotine in eliciting relevant receptor activation. Generally, typical compounds useful in carrying out the present invention effectively provide for the secretion of dopamine in amounts of at least about 50 percent, often at least about 75 percent, and frequently at least about 100 percent, of that maximally provided by (S)-(-)-nicotine. Certain compounds of the present invention can provide secretion of dopamine in an amount which can exceed that maximally provided by (S)-(-)-nicotine. Generally, typical compounds useful in carrying out the present invention are less potent than (S)-(-)-nicotine in eliciting neurotransmitter secretion, such as dopamine secretion.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, lack the ability to elicit activation of nicotinic receptors of human muscle to any significant degree. In that regard, the compounds of the present invention demonstrate poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from muscle preparations. Thus, such compounds exhibit receptor activation constants or EC₅₀ values (i.e., which provide a measure of the concentration of compound needed to activate half of the relevant receptor sites of the skeletal muscle of a patient) which are extremely high (i.e., greater than about 1mM). Generally, typical compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 5 percent of that maximally provided by (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause

-27-

significant activation of receptors associated with undesirable side effects. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder, is essentially 5 ineffective in eliciting activation of certain ganglionic-type nicotinic receptors. This selectivity of the compounds of the present invention against those receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those 10 compounds to activate nicotinic function of adrenal chromaffin tissue. As such, such compounds have poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from the adrenal gland. Generally, typical compounds useful 15 in carrying the present invention activate isotopic rubidium ion flux by less than 10 percent, often by less than 5 percent, of that maximally provided by S(-) nicotine.

Compounds of the present invention, when 20 employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, and amelioration to some degree of the 25 reoccurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as is demonstrated by decreased effects on preparations believed to reflect effects on the cardiovascular system, or effects to 30 skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention 35 is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects.

-28-

Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/5, and often less than 1/10, that amount sufficient to 5 cause any side effects to a significant degree.

The following example is provided in order to further illustrate various embodiments of the invention but should not be construed as limiting the scope thereof. Unless otherwise noted, all parts and 10 percentages are by weight.

EXAMPLE

Sample No. 1 is 5-ethoxy-metanicotine or (E)-N-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine, which was prepared essentially in accordance with the 15 following techniques:

3-Bromo-5-ethoxypyridine

3,5-Dibromopyridine (98%) was purchased from Lancaster Chemical Company. Sodium ethoxide (96%) and N,N-dimethylformamide (DMF) (99.9%, HPLC grade) were 20 purchased from Aldrich Chemical Company. Under a nitrogen atmosphere, a mixture of 3,5-dibromopyridine (5.00 g, 21.1 mmol), sodium ethoxide (2.87 g, 42.2 mmol), and DMF (10 mL) was stirred and heated at 65°C for 15 h. The mixture was poured into water (70 mL), 25 and anhydrous diethyl ether (155 mL) was added. Because of insoluble solids, it was necessary to filter both phases. The aqueous layer was separated and extracted with ether (2 x 25, 3 x 50 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and 30 concentrated by rotary evaporation, producing a dark-brown syrup. The brown residue was purified by vacuum distillation, affording 0.76 g (17.9%) of an oil, bp 105°C at 5 mm Hg. 1H NMR ($CDCl_3$): δ 9.12 (br s, 1H), 8.83 (br s, 1H), 8.42 (dd, 1H), 4.41 (q, 2H), 1.42

-29-

(t, 3H). ^{13}C NMR (CDCl_3): δ 142.72, 136.50, 123.78, 64.31, 14.57.

(E)-4-[3-(5-Ethoxypyridin)yl]-3-buten-1-ol

3-Buten-1-ol (99%) was purchased from Aldrich Chemical Company. Under a nitrogen atmosphere, a mixture of 3-buten-1-ol (144 mg, 2.0 mmol), 3-bromo-5-ethoxypyridine (424 mg, 2.1 mmol), palladium(II) acetate (5 mg, 0.02 mmol), tri-*o*-tolylphosphine (25 mg, 0.08 mmol), triethylamine (0.5 mL), and acetonitrile (1.0 mL) was stirred and heated under reflux for 21 h. Upon cooling, the mixture was diluted with water (10 mL) and extracted with methylene chloride (2 x 5 mL). The combined methylene chloride extracts were dried (Na_2SO_4), filtered, and concentrated via rotary evaporation to give a dark-yellow gum (423 mg). Purification by column chromatography on silica gel, eluting with methanol (2 --> 8%) in ethyl acetate afforded 256 mg (66.3%) of an almost colorless oil. ^1H NMR (CDCl_3): δ 8.15 (s, 1H), 8.12 (s, 1H), 7.14 (dd, 1H), 6.44 (d, 1H), 6.32-6.22 (dt, 1H), 4.06 (q, 2H), 3.77 (t, 2H), 2.49 (m, 2H), 1.42 (t, 3H). ^{13}C NMR (CDCl_3): δ 155.08, 140.48, 136.69, 133.46, 129.22, 129.00, 117.43, 63.87, 61.85, 36.43, 14.73.

(E)-N-Methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine

Under a nitrogen atmosphere, a cold (0°C), stirring solution of (E)-4-[3-(5-ethoxypyridin)yl]-3-buten-1-ol (240 mg, 1.24 mmol), methylene chloride (1 mL), and pyridine (1 drop) was treated with tosyl chloride (260 mg, 1.36 mmol). The mixture was allowed to warm to room temperature. After stirring for 12 h, the solution was concentrated by rotary evaporation. The resulting residue was dissolved in methanol (3 mL) and 40% aqueous methylamine (3 mL) was added. The solution was stirred 5 h at room temperature and was then concentrated by

-30-

rotary evaporation, affording the crude product (593 mg). The residue was partitioned between 1 M NaOH (2 mL) and chloroform (5 mL). The chloroform layer was separated, washed with water (2 mL), dried (Na_2SO_4),
5 filtered, and concentrated via rotary evaporation to give a dark oil (276 mg). The oil was purified by column chromatography on silica gel, eluting with triethylamine-methanol (2.5:97.5). Selected fractions were combined and concentrated via rotary evaporation
10 to give 87 mg (34.0%) of a light-brown oil, which quickly darkened. ^1H NMR (CDCl_3): δ 8.14 (d, 1H, $J=1.8$ Hz), 8.12 (d, 1H, $J=2.7$ Hz), 7.13 (dd, 1H, $J=2.8, 1.7$ Hz), 6.40 (d, 1H, $J=16.0$ Hz), 6.29-6.19 (dt, 1H, $J=16.0, 6.8$ Hz), 4.06, (q, 2H, $J=7.0$ Hz), 2.72 (t, 2H, $J=6.8$ Hz), 2.44 (s, 3H), 2.43 (dt, 2H, $J = 6.8$ Hz),
15 1.76 (br s, 1H), 1.41 (t, 3H, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3): δ 155.07, 140.48, 136.57, 133.59, 130.65, 128.09, 117.41, 63.85, 50.94, 36.14, 33.30, 14.72.

Sample No. 2 is (E)-N-methyl-5-(3-pyridinyl)
20 -4-penten-2-amine, which is prepared essentially in accordance with the following techniques:

5-(3-Pyridinyl)-4-penten-2-ol:

4-Penten-2-ol was purchased from Aldrich Chemical Company. Under a nitrogen atmosphere, a
25 mixture of 3-bromopyridine (3.0 g, 19 mmol), 4-penten-2-ol (1.69 g, 19.6 mmol), palladium (II) acetate (42.6 mg, 0.19 mmol), tri-*o*-tolylphosphine (116 mg, 0.38 mmol), and triethylamine (3.85 g, 38 mmol) was stirred at 90°C for 16 h. Triethylamine (1.45 g, 14 mmol) was added to the brown mixture which was allowed to stir an additional hour. The mixture was diluted with methylene chloride (20 mL) and water (20 mL). The aqueous phase was separated and extracted with methylene chloride (2 x 10 mL). The combined organic
30 phases were washed with 25 mL water, dried with Na_2SO_4 ,
35

-31-

filtered, and concentrated by rotary evaporation to give the compound as a dark yellow oil (3.05 g, 98%). Purification of the material was done by column chromatography on silica gel (225 g) eluting with

5 EtOAc-MeOH (4:1). Combined fractions containing 5-(3-pyridinyl)-4-penten-2-ol, as determined by TLC analysis yielded 2.69 g (88.2%) of a yellow oil.
TLC- (EtOAc-MeOH, 4:1): $R_f = 0.60$. ^1H NMR (CDCl_3 , 300 MHz): δ 8.55 (d, 1H), 8.42 (dd, 1H), 7.67 and 7.64 (dt, 1H), 7.23-7.18 (m, 1H), 6.44 (d, 1H), 6.33 and 6.27 (dt, 1H), 3.95 (m, 1H), 2.47-2.3 (m, 2H), 1.25 (d, 3H).

(E)-N-methyl-5-(3-pyridinyl)-4-penten-2-amine

Under a nitrogen atmosphere, methanesulfonyl chloride (2.02 g, 17.7 mmol) was added dropwise to a 15 stirring ice-cold solution of 5-(3-pyridinyl)-4-penten-2-ol (2.62 g, 16.1 mmol), triethylamine (3.25 g, 32.1 mmol) and tetrahydrofuran (THF) (5 mL). After one hour of stirring, additional THF (12 mL) and methanesulfonyl chloride (184 mg, 1.6 mmol) were added. The mixture was allowed to stir an additional 16 h. The dark-brown material was dissolved in water (50 mL), extracted with CHCl_3 (3 x 50 mL), dried (Na_2SO_4), filtered, and concentrated to give a mesylate (3.12 g, 80.6%) as a yellow oil. Methylamine (102 mL) was added to the mesylate (2.55 g, 10.6 mmol), and the mixture was allowed to stir at room temperature for ~ 17 h. The solution was basified with NaOH (one pellet) and extracted with diethyl ether (4 x 50 mL). The combined ether extracts were dried (Na_2SO_4), 30 filtered, and concentrated to a yellow syrup. Water (50 mL) was added to the residue. The pH was adjusted to 8.27 with concentrated HCl, and the solution was extracted with CH_2Cl_2 (3 x 25 mL) to remove impurities. The aqueous layer was separated, the pH was adjusted to 35 13.0 using 50% NaOH solution and the resulting solution was extracted with methyl tert-butyl ether (MTBE) (5 x

-32-

25 mL). The combined MTBE layers were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to yield 668 mg of a yellow oil. The oil (500 mg) was further purified by vacuum distillation to give 184.8 mg of an oil, bp 80°C at 0.05 mm Hg. Further purification by pH adjustment and extraction with MTBE and workup as described above afforded 127 mg (6.9%) of a yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 8.55 (d, 1H, $J=2.1$ Hz, H-2), 8.41 (dd, 1H, $J=1.6, 4.8$ Hz, H-6), 7.66 and 7.63 (dt, 1H, $J=2.0, 8.1$ Hz, H-4), 7.20 (m, 1H, $J=4.8, 1.5, 8.1$ Hz, H-5), 6.40 (d, 1H, $J=15.9$ Hz, H-5'), 6.28 and 6.23 (dt, 1H, $J=15.9, 7.0$ Hz, H-4'), 2.68 (m, 1H, $J=6.2$ Hz, H-2'), 2.41 (s, 3H, N-CH_3), 2.39-2.22 (m, 2H, $J=6.2, 7.0$ Hz, H-3'), 1.40 (br s, 1H, -NH) 1.08 (d, 3H, $J=6.2$ Hz, H-1'). ^{13}C NMR (CDCl_3 , 75MHz): δ 148.2 (C-6), 148.0 (C-2), 133.0 (C-3), 132.5 (C-4), 130.0 (C-4'), 128.8 (C-5'), 123.3 (C-5), 54.6 (C-2'), 40.5 (C-3'), 34.0 (C-1'), 19.9 (N-CH_3).
EI-MS: 175 (M^+).

20 Sample No. 3 is 5-methoxy-metanicotine or (E)-N-methyl-4-[3-(5-methoxypyridin)yl]-3-buten-1-amine, which was prepared essentially in accordance with the following techniques:

3-Bromo-5-methoxypyridine

25 This compound was prepared using the general procedure of Comins et al, J. Org. Chem., Vol. 55, pp. 69-73 (1990).

4-[(tert-Butyldimethylsilyl)oxy]-1-butene

Under a nitrogen atmosphere, to a cold (0°C), 30 stirring solution of 3-buten-1-ol (2.16 g, 30.0 mmol), pyridine (9 mL), and methylene chloride (30 mL) was added tert-butyldimethylsilyl chloride (4.53 g, 30.1 mmol) purchased from Aldrich Chemical Company. The ice-bath was removed and the mixture was allowed to

-33-

stir 1 h at room temperature. The mixture, containing a white precipitate, was poured into water (60 mL) and shaken. The methylene chloride layer was separated from the aqueous layer, and the aqueous layer extracted 5 with methylene chloride (30 mL). The two resulting organic extracts were combined, washed twice with water, dried (Na_2SO_4), filtered, and evaporated to give 8.94 g of crude product. Vacuum distillation afforded several fractions, the fraction with bp 80-82°C at 35 10 mm Hg was collected to give 3.14 g (56.3%) of product as an oil. ^1H NMR (CDCl_3): δ 5.86-5.73 (m, 1H), 5.08-4.98 (m, 2H), 3.64 (t, 2H), 2.29-2.22 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H).

(E)-4-[(tert-Butyldimethylsilyl)oxy]-1-[3-(5-methoxypyridin)yl]-1-butene

Under a nitrogen atmosphere, a mixture 15 4-[(tert-butyldimethylsilyl)oxy]-1-butene (745 mg, 4.0 mmol), 3-bromo-5-methoxypyridine (790 mg of 90 % purity, 4.2 mmol), palladium(II) acetate (10 mg, 0.045 20 mmol), tri-o-tolylphosphine (50 mg, 0.16 mmol), triethylamine (1.0 mL), and acetonitrile (2.0 mL) was stirred and heated under reflux for 20 h. Upon cooling, the mixture was diluted with water (20 mL) and extracted with methylene chloride (2 x 15 mL). The 25 combined methylene chloride extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated via rotary evaporation to give a brown oil (1.25 g, quantitative yield).

(E)-4-[3-(5-Methoxypyridin)yl]-3-buten-1-ol

30 A solution (E)-4-[(tert-butyldimethylsilyl)oxy]-1-[3-(5-methoxypyridin)yl]-1-butene (1.25 g, 4.00 mmol) in ethanol (5 mL) was treated at room temperature with 1 M HCl (5 mL). The solution was stirred for 20 min and then concentrated via rotary evaporation. 35 After further drying under high vacuum, the residue was

-34-

treated with saturated, aqueous NaHCO₃ solution (5 mL) and partitioned between water (20 mL) and ether (30 mL). The aqueous layer was separated, saturated with NaCl, and extracted with ether (20 mL). The combined
5 ether extracts were dried (Na₂SO₄), filtered, and then concentrated by rotary evaporation to give a viscous, yellow oil (632 mg). The product was purified by column chromatography on silica gel, eluting with methanol (3 --> 12%) in ethyl acetate. Selected
10 fractions were combined and concentrated via rotary evaporation to give 408 mg (56.9%) of an almost colorless oil. ¹H NMR (CDCl₃): δ 8.14 (s, 1H), 8.16 (s, 1H), 7.15 (dd, 1H), 6.32 (d, 1H), 6.33-6.23 (dt, 1H), 3.84 (s, 3H), 3.77 (t, 2H), 2.53-2.46 (m, 2H).

15 (E)-N-Methyl-4-[3-(5-methoxypyridin)yl]-3-buten-1-amine
Under a nitrogen atmosphere, a solution of (E)-4-[3-(5-methoxypyridin)yl]-3-buten-1-ol (387 mg, 2.16 mmol), methylene chloride (1 mL), and pyridine (2 drops) was cooled to (0°C). Tosyl chloride (433 mg, 2.27 mmol) was then added, and the solution was allowed to warm to room temperature. After stirring for 12 h, the solution was concentrated by rotary evaporation to a light-yellow gum (897 mg). The gummy residue was dissolved in methanol (4 mL) and 40% aqueous
20 methylamine (4 mL) was added. The solution was stirred 6 h at room temperature and was then concentrated by rotary evaporation. Further drying under high vacuum afforded a brown gum (936 mg). The residue was partitioned between 1 M NaOH (25 mL) and ether-THF
25 (1:1) (50 mL). The aqueous layer was separated and extracted with ether THF (1:1) (25 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated via rotary evaporation to give a dark-brown oil (432 mg). The oil was purified by
30 column chromatography on silica gel, eluting with triethylamine-methanol (2.5 : 97.5). Selected
35

-35-

fractions were combined and concentrated via rotary evaporation to give 180 mg (43.4%) of a dark-orange oil. ^1H NMR (CDCl_3): δ 8.16 (d, 1H, J = 1.8 Hz), 8.13 (d, 1H, J = 2.8 Hz), 7.14 (dd, 1H, J = 1.9 Hz), 6.41 5 (d, 1H, J = 16.0 Hz), 6.31-6.21 (dt, 1H, J = 16.0, 6.9 Hz), 3.84 (s, 3H), 2.73 (t, 2H, J = 6.8 Hz), 2.45 (s, 3H), 2.42 (dt, 2H, J = 6.8, 1.1 Hz), 1.62 (br s, 1H). ^{13}C NMR (CDCl_3): δ 155.69, 140.64, 136.19, 133.63, 130.99, 127.94, 116.70, 55.51, 51.09, 36.35, 33.51.

10 For comparison purposes, Sample No. C-1 was provided. This sample is (S)-(-)-nicotine, which has been reported to have demonstrated a positive effect towards the treatment of various CNS disorders.

15 For comparison purposes, Sample No. C-2 is (E)-metanicotine which was provided generally using the techniques set forth by Laforge, J.A.C.S., Vol. 50, p. 2477 (1928).

Determination of binding of compounds to relevant receptor sites

20 Rats (Sprague-Dawley) were maintained on a 12 hour light/dark cycle and were allowed free access to water and food supplied by Wayne Lab Blox, Madison, WI. Animals used in the present studies weighed 200 to 250 g. Brain membrane preparations were obtained from 25 brain tissue of either males or females.

Rats were killed by decapitation following anesthesia with 70% CO_2 . Brains were removed and placed on an ice-cold platform. The cerebellum was removed and the remaining tissue was placed in 10 volumes 30 (weight:volume) of ice-cold buffer (Krebs-Ringers HEPES: NaCl, 118 mM; KCl, 4.8 mM; CaCl_2 , 2.5 mM; MgSO_4 , 1.2 mM; HEPES, 20 mM; pH to 7.5 with NaOH) and homogenized with a glass-Teflon tissue grinder. The resulting homogenate was centrifuged at 18,000 x g for

-36-

20 min. and the resulting pellet was resuspended in 20 volumes of water. After 60 min. incubation at 4°C, a new pellet was collected by centrifugation at 18,000 x g for 20 min. After resuspension in 10 volumes of
5 buffer, a new final pellet was again collected by centrifugation at 18,000 x g for 20 min. Prior to each centrifugation step, the suspension was incubated at 37°C for 5 min. to promote hydrolysis of endogenous acetylcholine. The final pellet was overlaid with
10 buffer and stored at -70°C. On the day of the assay, that pellet was thawed, resuspended in buffer and centrifuged at 18,000 x g for 20 min. The pellet obtained was resuspended in buffer to a final concentration of approximately 5 mg protein/ml.
15 Protein was determined by the method of Lowry et al., J. Biol. Chem., Vol. 193, pp. 265-275 (1951), using bovine serum albumin as the standard.

The binding of L-[³H]nicotine was measured using a modification of the method of Romano et al.,
20 Science, Vol. 210, pp. 647-650 (1980) as described previously by Marks et al., Mol. Pharmacol., Vol. 30, pp. 427-436 (1986). The L-[³H]nicotine used in all experiments was purified chromatographically by the method of Romm, et al., Life Sci., Vol. 46, pp. 935-943
25 (1990). The binding of L-[³H]nicotine was measured using a 2 hr. incubation at 4°C. Incubations contained about 500 ug of protein and were conducted in 12 mm x 75 mm polypropylene test tubes in a final incubation volume of 250 ul. The incubation buffer was Krebs
30 Ringers HEPES containing 200 mM TRIS buffer, pH 7.5. The binding reaction was terminated by filtration of the protein containing bound ligand onto glass fiber filters (Micro Filtration Systems) that had been soaked in buffer containing 0.5 percent polyethyleneimine.
35 Filtration vacuum was -50 to -100 torr. Each filter was washed five times with 3 ml of ice-cold buffer. The filtration apparatus was cooled to 2°C before use

-37-

and was kept cold through the filtration process. Nonspecific binding was determined by inclusion of 10 μ M nonradioactive nicotine in the incubations.

The inhibition of L-[³H]nicotine binding by test compounds was determined by including one of eight different concentrations of the test compound in the incubation. Inhibition profiles were measured using 10 nM L-[³H]nicotine and IC₅₀ values were estimated as the concentration of compound that inhibited 50 percent of specific L-[³H]nicotine binding. Inhibition constants (Ki values), reported in nM, were calculated from the IC₅₀ values using the method of Cheng et al., Biochem. Pharmacol., Vol. 22, pp. 3099-3108 (1973).

Determination of Dopamine Release

Dopamine release was measured by preparing synaptosomes from the striatal area of rat brain obtained from Sprague-Dawley rats generally according to the procedures set forth by Nagy et al., J. Neurochem., Vol. 43, pp. 1114-1123 (1984). Striata from 4 rats were homogenized in 2 ml of 0.32M sucrose buffered with 5 mM HEPES (pH 7.5), using a glass-Teflon tissue grinder. The homogenate was diluted to 5 ml with additional homogenization solution and centrifuged at 1,000 \times g for 10 min. This procedure was repeated on the new pellet and the resulting supernatant was centrifuged at 12,000 \times g for 20 min. A 3 layer discontinuous Percoll gradient consisting of 16 percent, 10 percent and 7.5 percent Percoll in HEPES-buffered sucrose was made with the final pellet dispersed in the top layer. After centrifugation at 15,000 \times g for 20 min., the synaptosomes were recovered above the 16 percent layer with a Pasteur pipette, diluted with 8 ml of perfusion buffer (128 mM NaCl, 2.4 mM KCl, 3.2 mM CaCl₂, 1.2 mM KH₂PO₄, 1.2 mM MgSO₄, 25 mM HEPES pH 7.4, 10 mM dextrose, 1 mM ascorbate, 0.01 mM pargyline), and centrifuged at 15,000 \times g for 20 min.

-38-

The new pellet was collected and re-suspended in perfusion buffer. The synaptosome suspension was incubated for 10 min. at 37°C. [³H]-Dopamine (Amersham, 40-60 Ci/mmol) was added to the suspension to give a final concentration of 0.1 μ M, and the suspension was incubated for another 5 min. Using this method, 30 to 90 percent of the dopamine was taken up into the synaptosomes, as determined by scintillation counting following filtration through glass fiber filters soaked with 0.5 percent polyethyleneimine. A continuous perfusion system was used to monitor release following exposure to each ligand. Synaptosomes were loaded onto glass fiber filters (Gelman type A/E). Perfusion buffer was dripped onto the filters (0.2-0.3 ml/min.) and pulled through the filters with a peristaltic pump. Synaptosomes were washed with perfusion buffer for a minimum of 20 min. before addition of the ligand. After the addition of 0.2 ml of a solution containing various concentrations of ligand, the perfusate was collected into scintillation vials at 1 min. intervals and the dopamine released was quantified by scintillation counting. Peaks of radioactivity released above background were summed and the average basal release during that time was subtracted from the total. Release was expressed as a percentage of release obtained with an equal concentration of (S)-(-)-nicotine.

Determination of Log P

Log P values (log octanol/water partition coefficient), which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier (Hansch, et al., J. Med. Chem., Vol. 11, p. 1 (1968)), were calculated according to the methods described by Hopfinger, Conformational Properties of Macromolecules, Academic Press (1973)

-39-

using Cerius² software package by Molecular Simulations, Inc.

Determination of Interaction with Muscle

Human muscle activation was established on
5 the human clonal line TE671/RD which is derived from an
embryonal rhabdomyosarcoma (Stratton et al.,
Carcinogen, Vol. 10, pp. 899-905 (1989)). As evidenced
through pharmacological (Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp. 175-182 (1989)),
10 electrophysiological (Oswald et al, Neurosci. Lett., Vol. 96, pp. 207-212 (1989)), and molecular biological
studies (Luther et al., J. Neurosci., Vol. 9, pp.
1082-1096 (1989)) these cells express muscle like
nicotinic receptors. Nicotinic acetylcholine receptor
15 (nAChR) function was assayed using ⁸⁶Rb⁺ efflux
according to a method described by Lukas et al., Anal. Biochem, Vol. 175, pp. 212-218 (1988). Dose-response
curves were plotted and the concentration resulting in
half maximal activation of specific ion flux through
20 nicotinic receptors determined for human muscle and rat
ganglionic preparations (EC50). The maximal activation
for individual compounds (Emax) was determined as a
percentage of the maximal activation induced by
(S)-(-)-nicotine.

25 Determination of Interaction with Ganglia

Ganglionic effects were established on the
rat pheochromocytoma clonal line PC12, which is a
continuous clonal cell line of neural crest origin
derived from a tumor of the rat adrenal medulla
30 expressing ganglionic-type neuronal nicotinic receptors
(see Whiting et al., Nature, Vol. 327, pp. 515-518
(1987); Lukas, J. Pharmacol. Exp. Ther., Vol. 251, pp.
175-182 (1989); Whiting et al., Mol. Brain Res., Vol.
10, pp. 61-70 (1990)). Discussion concerning the
35 heterogeneity of nicotinic receptors subtypes is set

-40-

forth in Lukas et al., Internat'l. Review Neurobiol., Vol. 34, pp. 25-130 (1992). Acetylcholine nicotinic receptors expressed in rat ganglia share a very high degree of homology with their human counterparts. See,
5 Fornasari et al., Neurosci. Lett., Vol. 111, pp. 351-356 (1990) and Chini et al., Proc. Natl. Acad. Sci. USA, Vol. 89, pp. 1572-1576 (1992). Both clonal cell lines described above were maintained in proliferative growth phase according to routine protocols (Bencherif
10 et al., Mol. Cell. Neurosci., Vol. 2, pp. 52-65, (1991) and Bencherif et al., J. Pharmacol. Exp. Ther., Vol. 257, pp. 946-953 (1991)). Intact cells on dishes were used for functional studies. Routinely, sample aliquots were reserved for determination of protein
15 concentration using the method of Bradford, Anal. Biochem., Vol. 72, pp. 248-254 (1976) with bovine serum albumin as the standard.

Nicotinic acetylcholine receptor (nAChR) function was assayed using $^{86}\text{Rb}^+$ efflux according to a
20 method described by Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988). Cells were plated in 35-mm diameter wells of 6-well dishes for at least 48 hours and loaded for at least 4 hours at 37°C in a medium containing serum, and 1 $\mu\text{Ci}/\text{ml}$ $^{86}\text{Rb}^+$. Following removal
25 of the loading medium, cells were quickly washed three times with label-free Ringer's solution and exposed for 4 minutes at 20°C to 900 μl of Ringer's containing the indicated concentration of compound to be tested (to define total efflux) or in addition to 100 μM mecamylamine (to define non-specific efflux). The
30 medium was removed and $^{86}\text{Rb}^+$ was quantitated using Cerenkov detection (see Lukas et al., Anal. Biochem., Vol. 175, pp. 212-218 (1988)). Specific ion efflux was determined as the difference in isotope efflux between
35 total and non-specific efflux samples. Dose-response curves were plotted and the concentration resulting in half maximal activation of specific ion flux through

-41-

nicotinic receptors determined for human muscle and rat ganglionic preparations (EC50). The maximal activation for individual compounds (Emax) was determined as a percentage of the maximal activation induced by
5 (S)-(-)-nicotine.

Determination of ion flux from thalamic synaptosomes

Rat brains were dissected and midbrain (thalamus and mesencephalon) removed. The midbrain was then placed into a tube on ice, homogenized, and
10 centrifuged at 2800 rpm for 10 minutes. The supernatant was collected and centrifuged for another 20 minutes at 9650 rpm. The resulting pellet was resuspended by trituration in 700 μ l ice cold perfusion buffer. Synaptosomes were then loaded with $^{86}\text{Rb}^+$ Ion
15 efflux was determined using the methods of Marks et al., J. Pharmacol. Exp. Ther., Vol. 264, pp. 427-436 (1993). Total efflux was determined by subtraction of basal release from release at stimulation (total peak release). The ratio of the peak to baseline (Rp) was
20 calculated for each concentration. A tetramethylammonium control (i.e., a full agonist to the receptor of interest) is used in each assay to compare each agonist's ability to stimulate rubidium efflux to the control. Emax values are reported as a
25 percent of Emax for tetramethylammonium.

Data are presented in Table I.

-42-

TABLE ISample No.

		1	2	3	C-1*	C-2*
5	Ki (nm)	9	82	7	4	26
	log P	2.37	2.24	1.84	0.71	1.39
	Receptor Activation					
	Emax (%)	67	35	62	87	79
10	EC50 (nm)	269	1,700	470	591	732
	Dopamine Release					
	Emax (%)	124	182	106	100	81
	EC50 (nm)	287	21,400	2,341	100	1,158
	Muscle Effect					
15	Emax (%)	0	4	0	100	0
	EC50	NM	NM	NM	80,000	NM
	Ganglion Effect					
	Emax (%)	0	6	0	100	0
	EC50	NM	NM	NM	20,000	NM

20 * not an example of the invention

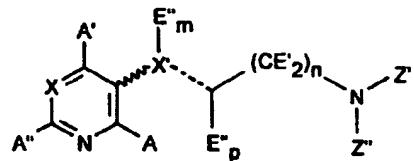
NM not meaningful, due to lack of effect

The data in Table I indicate that the compounds have the capability of passing the blood-brain barrier by virtue of their favorable log P values, binding to high affinity CNS nicotinic receptors as indicated by their low binding constants, and activating CNS nicotinic receptors of a subject and causing neurotransmitter release, thereby demonstrating known nicotinic pharmacology. Thus, the data indicate that such compounds have the capability of being useful in treating CNS disorders involving nicotinic cholinergic systems. Furthermore, the data indicate that the compounds do not cause any appreciable effects at muscle sites and ganglionic sites, thus indicating a lack of undesirable side effects in subjects receiving administration of those compounds.

-43-

CLAIMS:

1. A compound having the formula:



where X is nitrogen or carbon bonded to a substituent species characterized as having a sigma m value between 5 about -0.3 and about 0.75; n is 1, 2, 3, 4, 5, 6 or 7; Z' and Z'' individually represent hydrogen, alkyl containing one to five carbon atoms; A, A' and A'' individually represent hydrogen, alkyl containing one to seven carbon atoms, or halo; the dashed line in the 10 structure represents a C-C single bond, a C-C double bond or a C-C triple bond; m is 0 or 1 when the dashed line represents a C-C single bond or a C-C double bond, and m is 0 when the dashed line represents a C-C triple bond; p is 0 or 1 when the dashed line represents a C-C single bond or a C-C double bond, and p is 0 when the 15 dashed line represents a C-C triple bond; the wavy line in the structure represents a cis(Z) or trans(E) form of the compound when the dashed line in the structure is a C-C double bond; and E' and E'' individually 20 represent hydrogen, alkyl containing one to five carbon atoms or halo-substituted alkyl containing one to five carbon atoms.

2. A compound selected from the group consisting of (E) and (Z)-N-methyl-4-(3-pyridinyl)-2-methyl-3-buten-1-amine, 25 (E) and (Z)-N-methyl-4-(3-pyridinyl)-3-methyl-3-buten-1-amine, (E) and

-44-

(Z)-N-methyl-6-(3-pyridinyl)-5-hexen-3-amine, (E) and
(Z)-N-methyl-5-(3-pyridinyl)-2-methyl-4-penten-2-amine,
(E) and (Z)-N-methyl-5-(3-pyridinyl)-3-methyl
-4-penten-2-amine, (E) and (Z)-N-methyl-5-(3-pyridinyl)
5 -4-penten-2-amine, (E) and (Z)-N-methyl-5-(3
-pyridinyl)-1,1,1-trifluoro-4-penten-2-amine, (E) and
(Z)-N-methyl-5-(3-pyridinyl)-4-methyl-4-penten-1-amine,
(E) and (Z)-N-methyl-5-(3-pyridinyl)
-4-methyl-4-penten-2-amine, (E) and (Z)-N-methyl-8-(3-
10 pyridinyl)-7-octen-5-amine, (E) and
(Z)-N-methyl-7-(3-pyridinyl)-3-methyl-6-hepten-4-amine,
(E) and (Z)-N-methyl-6-(3-pyridinyl)
-2,4-dimethyl-5-hexen-2-amine, (E) and
(Z)-N-methyl-6-(3-pyridinyl)-5-methyl-5-hexen-2-amine,
15 (E) and (Z)-N-methyl-6-(3-pyridinyl)-5-hexen-2-amine,
(E) and (Z)-N-methyl-6-(3-pyridinyl)-5-methyl-5-
hexen-3-amine, (E) and
(Z)-4-(3-pyridinyl)-2-methyl-3-buten-1-amine, (E) and
(Z)-4-(3-pyridinyl)-3-methyl-3-buten-1-amine, (E) and
20 (Z)-6-(3-pyridinyl)-5-hexen-3-amine, (E) and
(Z)-5-(3-pyridinyl)-2-methyl-4-penten-2-amine, (E) and
(Z)-5-(3-pyridinyl)-3-methyl-4-penten-2-amine, (E) and
(Z)-5-(3-pyridinyl)-4-penten-2-amine, (E) and
(Z)-5-(3-pyridinyl)-1,1,1-trifluoro-4-penten-2-amine,
25 (E) and (Z)-5-(3-pyridinyl)-4-methyl-4-penten-1-amine,
(E) and (Z)-5-(3-pyridinyl)-4-methyl-4-penten-2-amine,
(E) and (Z)-8-(3-pyridinyl)-7-octen-5-amine, (E) and
(Z)-7-(3-pyridinyl)-3-methyl-6-hepten-4-amine, (E) and
(Z)-6-(3-pyridinyl)-2,4-dimethyl-5-hexen-2-amine, (E)
30 and (Z)-6-(3-pyridinyl)-5-methyl-5-hexen-2-amine, (E)
and (Z)-6-(3-pyridinyl)-5-hexen-2-amine, and (E) and
(Z)-6-(3-pyridinyl)-5-methyl-5-hexen-3-amine.

3. A compound selected from the group
consisting of

35 N-methyl-4-(3-pyridinyl)-2-methyl-butan-1-amine,
N-methyl-4-(3-pyridinyl)-3-methyl-butan-1-amine,

-45-

N-methyl-6-(3-pyridinyl)-hexan-3-amine,
N-methyl-5-(3-pyridinyl)-2-methyl-pantan-2-amine,
N-methyl-5-(3-pyridinyl)-3-methyl-pantan-2-amine,
N-methyl-5-(3-pyridinyl)-pentan-2-amine,
5 N-methyl-5-(3-pyridinyl)-1,1,1-trifluoro-pantan-2-amine
, N-methyl-5-(3-pyridinyl)-4-methyl-pantan-1-amine,
N-methyl-5-(3-pyridinyl)-4-methyl-pantan-2-amine,
N-methyl-8-(3-pyridinyl)-octan-5-amine,
N-methyl-7-(3-pyridinyl)-3-methyl-heptan-4-amine,
10 N-methyl-6-(3-pyridinyl)-2,4-dimethyl-hexan-2-amine,
N-methyl-6-(3-pyridinyl)-5-methyl-hexan-2-amine,
N-methyl-6-(3-pyridinyl)-hexan-2-amine,
N-methyl-6-(3-pyridinyl)-5-methyl-hexan-3-amine,
4-(3-pyridinyl)-2-methyl-butan-1-amine,
15 4-(3-pyridinyl)-3-methyl-butan-1-amine,
6-(3-pyridinyl)-hexan-3-amine,
5-(3-pyridinyl)-2-methyl-pantan-2-amine,
5-(3-pyridinyl)-3-methyl-pantan-2-amine,
5-(3-pyridinyl)-pentan-2-amine,
20 5-(3-pyridinyl)-1,1,1-trifluoro-pantan-2-amine,
5-(3-pyridinyl)-4-methyl-pantan-1-amine,
5-(3-pyridinyl)-4-methyl-pantan-2-amine,
8-(3-pyridinyl)-octan-5-amine,
7-(3-pyridinyl)-3-methyl-heptan-4-amine,
25 6-(3-pyridinyl)-2,4-dimethyl-hexan-2-amine,
6-(3-pyridinyl)-5-methyl-hexan-2-amine,
6-(3-pyridinyl)-hexan-2-amine and
6-(3-pyridinyl)-5-methyl-hexan-3-amine.

4. A compound selected from the group
30 consisting of
N-methyl-5-(3-pyridinyl)-4-pentyn-2-amine,
N-methyl-6-(3-pyridinyl)-5-hexyn-3-amine,
N-methyl-7-(3-pyridinyl)-6-heptyn-4-amine,
N-methyl-8-(3-pyridinyl)-7-octyn-5-amine,
35 N-methyl-9-(3-pyridinyl)-8-nonyn-6-amine,
N-methyl-5-(3-pyridinyl)-3-methyl-4-pentyn-2-amine,

-46-

5- (3-pyridinyl)-4-pentyn-2-amine,
6- (3-pyridinyl)-5-hexyn-3-amine,
7- (3-pyridinyl)-6-heptyn-4-amine,
8- (3-pyridinyl)-7-octyn-5-amine,
5 9- (3-pyridinyl)-8-nonyn-6-amine and
5- (3-pyridinyl)-3-methyl-4-pentyn-2-amine.

5. The compound of Claim 1 wherein the wavy line is a C-C double bond and the compound has a trans (E) form.

10 6. The compound of Claim 1 wherein n is 1, 2, 3 or 4.

7. The compound of Claim 1 wherein n is 1, 2 or 3; Z' and Z'' individually represent hydrogen, methyl or isopropyl; A and A' represent hydrogen; and 15 A'' represents hydrogen, methyl, ethyl or halo.

8. The compound of Claim 7 wherein the wavy line is a C-C double bond and the compound has a trans (E) form.

9. The compound of Claim 1 wherein X is 20 -CH.

10. The compound of Claim 6 wherein A, A' and A'' each are hydrogen.

11. The compound of Claim 1 wherein E' and E'' are methyl.

25 12. The compound of Claim 1 wherein m=0 and p=0.

13. The compound of Claim 1 wherein Z' is hydrogen and Z'' is methyl.

-47-

14. The compound of Claim 1 wherein n is 2
or 3.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/06398

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/38 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 684 654 A (W. B. WRIGHT) 4 August 1987 see example 29; table VII ---	1
X,P	US 5 616 716 A (DULL GARY M ET AL) 1 April 1997 see the whole document ---	1-14
X,P	WO 96 20600 A (REYNOLDS TOBACCO CO R ;BENCHERIF MEROUANE (US); LIPPIELLO PATRICK) 11 July 1996 see claims 16-19 ---	1-14
X,P	WO 96 20929 A (REYNOLDS TOBACCO CO R ;UNIV KENTUCKY RES FOUND (US); CROOKS PETER) 11 July 1996 see claims 1-5; examples ---	1-14
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

1 Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1997	18.08.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentstaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Bosma, P

INTERNATIONAL SEARCH REPORTInternational Application No
PCT/US 97/06398

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 8, 1989, WASHINGTON US, pages 1820-1835, XP002037072 R.W. GUTHRIE ET AL.: "Pentadienyl carboxamide derivatives as antagonists of platelet-activating factor" see compounds 88-90 on page 1820 -----	1, 3

1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/06398

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. Claims Nos.: 1 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In claim 1 a vast number of known compounds is claimed. More than 90 separate novelty destroying documents could be cited. The present search report provides only a sample of them.
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/06398

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4684654 A	04-08-87	EP 0293500 A JP 63316778 A	07-12-88 26-12-88
US 5616716 A	01-04-97	NONE	
WO 9620600 A	11-07-96	US 5597919 A AU 4610896 A	28-01-97 24-07-96
WO 9620929 A	11-07-96	US 5616707 A AU 4645596 A	01-04-97 24-07-96